

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Ulf TILSTAM et al.

Examiner: Elli PESELEV

Serial No.: 09/471,040

Group Art Unit: 1623

Filed: December 23, 1999

Title: PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS AND PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST 99.5%

**REPLY**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

The following is responsive to the office action of February 7, 2007.

The examiner alleges it would be obvious to apply the purification method mentioned in columns 5 and 6 of Butler (for the unfluorinated version of the compound of the claims of this application) to the fluorinated product produced by the process of Blumbergs in order to obtain a product of higher purity. However, this line of reasoning completely ignores the explicit warning in Blumbergs not to apply processes such as that of Butler in an effort to purify the Blumbergs product (fludarabine phosphate). Blumbergs state the following in the paragraph bridging columns 10 and 11:

In view of the extensive handling in the last step, a final recrystallization was necessary to remove any inadvertently-introduced water-insoluble impurities. The acidic product is, however, unstable in hot water. Some decomposition occurs during the recrystallization and no real improvement in purity results. With careful handling in the last step, it is possible that the final recrystallization can be avoided.

See also US 5,296,589, col. 9, lines 60-68, stating the same.

As can be seen, recrystallization of fludarabine phosphate leads to “no real improvement in purity results.” Moreover, recrystallization is to be avoided by careful handling. Consequently, this constitutes a very strong statement that purification processes involving recrystallization should not be employed because they will provide no real improvement in purity.

However, the purification technique relied on by the examiner from column, line 44 to column 6, line 19 of Butler et al. is precisely a recrystallization method. Thus, it is unambiguous that a skilled worker would not be motivated to apply the Butler et al. recrystallization technique to purify the fludarabine phosphate obtained by Blumbergs.

That the Butler process is a recrystallization technique, is clear from the described chemistry. The Butler compound is dissolved in water under ammonium hydroxide neutralization conditions. See column 5, lines 59-66. Note line 65-66: “until solution is essentially complete.” (emphasis added) Subsequently, the solution is treated with concentrated hydrochloric acid and ethanol which results in crystallization occurring. See column 6, lines 1-7, particularly line 6 explicitly mentioning that “crystallization occurs.” Clearly, Butler’s compound is subjected to dissolution/crystallization, in other words, recrystallization. This is exactly what Blumbergs says not to do for its compound, i.e., fludarabine phosphate.

Thus, the examiner’s combination of references explicitly states that the references should not be combined in the way the examiner proposes. On this basis alone, the rejection can be seen to be untenable and must be withdrawn. Moreover, as established of record (see, e.g., the Wessa and Rabe Declaration under 37 CFR §1.132 and the quoted passage from Blumbergs), the fluorinated version of the Butler compound is highly unstable under very many conditions. There is nothing in Butler which indicates that its compound is unstable or that its recrystallization purification process is for some reason applicable to unstable compounds, even those for which recrystallization is said to be avoided in the prior art.

Furthermore, with respect to the claims of this application reciting the purity of at least 99.5%, the purity achieved by Butler et al., which is only 94.81% (column 6, line 19), would be further motivation for its avoidance, were such needed.

Finally, even in one unreasonably alleged that, despite all the foregoing, it would still be reasonable for a skilled worker to combine the Butler et al. recrystallization process with the

product of Blumbergs, experimental data of record show that, as expected from Blumberg's statement, the instability of fludarabine phosphate would preclude achievement of sufficient purity to arrive at that recited in the claims. Note, for example, pages 18-19 of the Wessa and Rabe Declaration. These data show that at acidic pH's for a time of one week at a pH of 3, the sum of contaminants rises from 0.91 wt% to 18.77 wt%. Under the 1-2 day hold time reported in Butler et al. for the pH condition of  $2.5 \pm 0.1$  (column 6, lines 1-8), this results in a contamination increase of at least 2.55 for even a 1 day hold time  $((18.77-0.91) \div 7)$ . This, of course, brings the impurity level far beyond that permitted by the claims.

Consequently, as can be seen, there is no absolutely no motivation to combine the references as alleged by the examiner. In fact, a fair reading of the two references establishes strong reasons not to apply the recrystallization technique of Butler et al. to purify the fludarabine phosphate of Blumbergs et al. Even if one ignored this lack of motivation, scientific data of record establishes that the combination cannot lead to the requisite purity recited in the claims.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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